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CLAIMS

(57) [Claim(s)]
[Claim 1] The manufacture approach of the reforming hollow filament characterized by constructing a bridge in this hydrophilic high polymer after [the semipermeable hollow filament used for hemodialysis, a protein fraction, or plasma skimming] contacting a hydrophilic high polymer to an internal surface at least.
[Claim 2] The manufacture approach of the reforming hollow filament according to claim 1 characterized by the approach of constructing a bridge being radiation-induced crosslinking.
[Claim 3] The reforming hollow filament characterized by holding physically the hydrophilic high polymer which is the reforming hollow filament obtained by the manufacture approach according to claim 1 or 2, and was insolubilized to water near [the] the front face.
[Claim 4] The reforming hollow filament according to claim 3 characterized by a reforming hollow filament being a cellulose system hollow filament.
[Claim 5] The reforming hollow filament according to claim 4 characterized by hydrophilic polymeric materials being a polyvinyl pyrrolidone and/or a polyethylene glycol.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[0001]
[0002]
[Industrial Application] This invention relates to the hollow filament by which reforming was carried out, and its manufacture approach. Furthermore, it is related with the reforming hollow filament biocompatibility and whose haemocompatibility improved, and its manufacture approach in detail by making the hydrophilic high polymer of a semipermeable hollow filament which insolubilized in water to the internal surface at least hold physically.
[0003]
[0002]
[0004]
[Description of the Prior Art] The technique of using the film which has alternative permeability progresses splendidly in recent years, and utilization in extensive fields, such as a separation filter of a gas or a liquid, hemodialyzer in the medical field, a hemofiltration machine, and a constituent-of-blood selection separation filter, is progressing.
[0005]
[0003] Since especially the hollow filament-like film can make small occupied volume per film surface product, it miniaturizes andis [lightweight-] easy toize it, and it is used suitably. As a film ingredient, polymers, such as cellulose systems (a regenerated-cellulose system, a cellulose acetate system, chemistry denaturation cellulose system, etc.), a polyacrylonitrile system, a polymethylmethacrylate system, an ethylene vinyl alcohol system, and a polyamide system, have been used.
[0006]
[0004]
[0007]
[Problem(s) to be Solved by the Invention] However, when contacting the hollow filament used conventionally into blood, it is known by extent with the thick ingredient that a difference will occur a vital reaction between the constituent of blood of a certain thing of a certain kind and a film front face.
[0008]
[0005] For example, in the case of a cellulose system hollow filament, the alternative pathway of complement is activated, and when C3a which is anaphylatoxin is made to generate or it is used as a dialyzer, temporary reduction of the leucocyte in peripheral blood liquid is caused.
[0009]
[0006] In the case of a polyacrylonitrile system hollow filament, giant-molecule kininogen is activated. and it is said that bradykinin is generated.
[0010]
[0007] the elastase which is the protease which there are many amounts of adhesion of a platelet in the case of a polymethylmethacrylate system hollow filament, is said for blood to tend to remain in the

hollow filament after extracorporeal circulation termination of blood when it uses as a dialyzer, and occurs emission of granulocyte -- dialysis -- the crown -- becoming a value is also known.
[0011]
[0008] It is indicated that there is activation of complement classical pathway in the case of an ethylene vinyl alcohol system hollow filament.
[0012]
[0009] In the case of a polyamide system hollow filament, there are many amounts of adhesion of a platelet too, and there are many amounts of blood residuals into a hollow filament.
[0013]
[0010] Thus, when the hollow filament used from the former was used as it was, the vital reaction occurred between a certain kind of constituent of blood, and the film front face, it has had a bad influence on it to blood not a little, and, for that reason, fewer hollow filaments of the vital reaction to a constituent of blood were desired.
[0014]
[0011]
[0015]
[Means for Solving the Problem] this invention persons solve the trouble which the hollow filament which exists from the above-mentioned former has. The result of having repeated research wholeheartedly in order to obtain fewer hollow filaments of the vital reaction on a certain kind of constituent of blood, and the front face of a hollow fiber, By making the hydrophilic high polymer of a semipermeable hollow filament which insolubilized in water to the internal surface (front face in contact with blood) at least hold physically, it came to constitute a header and this invention for the vital reaction of a constituent of blood and an internal surface being improved a surprising degree.
[0016]
[0012] That is, this invention is a semipermeable hollow filament, and about the reforming hollow filament characterized by holding physically the hydrophilic high polymer insolubilized by the internal surface to water at least, after [a semipermeable hollow filament] contacting a hydrophilic high polymer to an internal surface at least, it relates to the manufacture approach of the reforming hollow filament characterized by constructing a bridge in this hydrophilic high polymer.
[0017]
[0013] Especially with the semipermeable hollow filament said here, by what is limited by the ingredient, a configuration, a dimension, the fractionation property, etc., there is nothing and hemodialysis, a protein fraction, plasma skimming, etc. should just choose a suitable thing in the light of the purpose.
[0018]
[0014] If an ingredient is illustrated, polymers, such as cellulose systems, such as a regenerated-cellulose system, a cellulose acetate system, and a chemistry denaturation cellulose system, a polyacrylonitrile system, a polymethylmethacrylate system, a polyvinyl system containing an ethylene-vinylalcohol copolymer, a polyamide system, a polyester system, and a polyolefine system, are mentioned, especially, a cellulose system polymer will have a strong mechanical strength, and thin-film-izing of a hollow fiber will be possible for it, and it will be used suitably.
[0019]
[0015] Although a cylinder-like object is usually used, a configuration The object of the configuration where the fin was attached to the cylindrical lateral surface can also be used. A dimension Thickness can use 5-50 micrometers and a bore can use preferably 1-100 micrometers of 50-500 micrometers of about 100-300-micrometer objects. About a fractionation property By the application, if it is an object for dialysis, if the permeability of the matter of molecular weight smaller than albumin is a high hollow filament and an object for protein fractions, low-molecular protein will penetrate from the low-molecular-weight matter. If it is the hollow filament and the object for plasma skimming which neither macromolecule protein nor matter like an immune complex can penetrate easily, although a plasma component will be penetrated, the hollow filament which does not penetrate a corpuscle component is

used suitably.
[0020]
[0016] Moreover, although the matter which is meltable in water as for a hydrophilic high polymer, and constructs a bridge by physical processing and/or chemical preparation, and can insolubilize [as opposed to / by that cause / water] is said and ******, a polyvinyl pyrrolidone, a polyethylene glycol, polyvinyl alcohol, a polypropylene glycol, etc. are mentioned, it is not limited to these, and it can recommend especially from the field of a biocompatibility improvement of a polyvinyl pyrrolidone and/or a polyethylene glycol in these.
[0021]
[0017] Viscosity although bridge formation tended to progress, when the larger one makes it a water solution becomes high, and it is hard coming to deal with the molecular weight of a hydrophilic high polymer. therefore -- as those molecular weight -- 500 to 1 million -- they are 10,000 to 500,000, and the thing which 20,000 to 400,000 can recommend still more preferably preferably.
[0022]
[0018] It is [of being divided] **** in the solubility over water that a hydrophilic high polymer is insolubilized to water, as a result of constructing a bridge over the above-mentioned hydrophilic high polymer and macromolecule-izing further.
[0023]
[0019] Moreover, that a hydrophilic high polymer is held physically at least at the internal surface The hydrophilic high polymer insolubilized to water exists near the front face of a semipermeable hollow filament. The hydrophilic high polymer underwater insolubilized to elution, the condition not separating, and which is held like, or water infiltrates into the interior of a semipermeable hollow filament in part. Without saying the condition of being mechanically held near the semipermeable hollow filament front face, and limiting a hydrophilic macromolecule's existence part only to an internal surface, even if it exists in parts other than this, for example, an outside surface, it does not interfere.
[0024]
[0020] The approach of contacting a hydrophilic high polymer to a semipermeable hollow filament A hydrophilic high polymer is contacted to the back semipermeable hollow filament dissolved in water, suitable solvents, or these mixed solvents. The approach of blowing away a solution excessive after that with a gas, the method of spraying the hydrophilic polymer solution which made it the shape of a fog on a semipermeable hollow filament, etc., Processing which could use the well-known coating approach and was described above may be performed in the state of a hollow filament, and you may carry out, after changing a hollow filament into the condition of modules, such as a dialyzer, a protein fraction Mr. filter, etc. with which the container was filled up.
[0025]
[0021] Although the concentration of a hydrophilic polymer solution can be chosen as arbitration in consideration of the filtration efficiency of the solution viscosity when carrying out to the molecular weight of a hydrophilic high polymer, i.e., a solution, and the semipermeable hollow filament after bridge formation etc., 0.1 to 1% of the weight of solution concentration can recommend [0.05] it still more preferably 5% of the weight preferably 10% of the weight from 0.01.
[0026]
[0022] If the approach of making a hydrophilic high polymer constructing a bridge is illustrated, in order to mention the radiation-induced crosslinking method using a gamma ray, an X-ray, etc., an ultraviolet-rays cross-linking method, a heat cross-linking method, the approaches using a crosslinking reagent, or such combination and to promote bridge formation, Various initiators, an initiation assistant or a polymerization nature monomer, oligomer, a polymer, etc. can also be used, and since there is little effect which it has on the membrane structure of a semipermeable hollow filament among the above-mentioned cross-linking methods and there are few problems of a residual reagent, especially a radiation-induced crosslinking method can recommend.
[0027]
[0023] Although selection of the dosage can select extent of bridge formation of a hydrophilic

macromolecule, and extent of degradation of a material to a scale at arbitration when using a gamma ray among radiation-induced crosslinking methods, it is the dosage which 10 to 25kG(ics) can recommend still more preferably 50 kGies from 5 preferably 100 kGies from 1.
[0028]
[0024] As for the reforming hollow filament of this invention, it is common that the a large number book is used for a container in the form of the module by which adhesion immobilization was carried out, and it ** and explains it to drawing 1 hereafter taking the case of a dialyzer. Although drawing 1 is the mimetic diagram showing an example of a dialyzer, the a large number book converges on the dialysing fluid entrance 5 and the container 2 which has 5', an edge pastes up by potting material 3 like urethane, and the reforming hollow filament 1 is fixed to a container.
[0029]
[0025] A part for the centrum of the reforming hollow filament 1 is wide opened by a blood access 4 and 4', blood has the structure of flowing the inside of a reforming hollow filament, and the number of the reforming hollow filament 1 does not have them here what is limited to this range, although 1000 to 20000 and effective length have the common range of 150 to 400mm. Dialysing fluid enters from inlet-port 5', contacts the outside surface of the reforming hollow filament 1, and is discharged from an outlet 5, and the usage of blood of being discharged from the back outlet 4 which entered from inlet-port 4', entered in the reforming hollow filament 1, and was dialyzed is common. Although blood contacts the inside of the reforming hollow filament 1 The frequency where the front face and blood of the ingredient itself of the semipermeable hollow filament structure contact directly since the layer of a hydrophilic high polymer is formed in reforming hollow filament 1 internal surface is stopped low. As the result When the vital reaction of the fault which it is thought that the vital reaction between blood - film ingredients is controlled by it a surprising degree, consequently each film ingredient front face has, i.e., blood, has been improved, the fractionation property which each film ingredient has can be demonstrated enough.
[0030]
[0026]
[0031]
[Example]
The dialyzer shown in drawing 1 , using a cuprammonium rayon ammonium cellulose hollow filament as examples 1-6 and an example of comparison 1 semipermeable hollow filament was made as an experiment.
[0032]
[0027] this dialyzer -- the thickness of 15 micrometers of a hollow filament, the bore of 180 micrometers, and the number of filaments -- 11000 and film surface product 1.5m2 it is -- to this dialyzer, polyvinyl-pyrrolidone (Following PVP is called.) processing was performed as a hydrophilic polymeric material, and it considered as examples 1-6. The processing condition is shown in Table 1.
[0033]
[0028]
[0034]
[Table 1]

	PVP 分子量	PVP濃度 (重量%)	γ線線量 (kGy)
実施例1	4万	0.1	10
実施例2	4万	1.0	10
実施例3	4万	5.0	10
実施例4	36万	0.02	10
実施例5	36万	0.1	10
実施例6	36万	1.0	10

PVP used the thing of molecular weight 40,000 and molecular weight 360,000, and prepared the water solution of the concentration shown in Table 1, respectively. After pouring 200ml of each PVP solutions from blood inlet-port 4' to each unsettled dialyzer by the 800ml rate of flow for /, the PVP solution which remains by the 0.2kg/cm2 compressed air was blown away, and it discharged from the blood outlet 4. The gamma ray of next 10kGy was irradiated. Next, it was filled up with the inside of a hollow filament, and an outside, i.e., the container 2 interior, with water, and considered as the dialyzer of examples 1-6.

[0035]

[0029] On the other hand, the dialyzer which does not perform PVP processing was made into the example 1 of a comparison.

[0036]

[0030] The following trials were performed about the examples 1-6 and the example 1 of a comparison which were created as mentioned above.

[0037]

[0031] 1). In accordance with the performance-evaluation criteria of Japanese Society for Artificial Organs, the path clearance (value at the time of pressure 0mmHg between film) of the amount of water penetration (the unit omitted Following uFR is ml/hr/mmHg), a creatinine, and vitamin B12 (henceforth, VB 12) was measured.

[0038]

[0032] 2). According to the performance-measurement criteria of Japanese Society for Artificial Organs, the path clearance (however, value at the time of pressure 0mmHg between film) of a myoglobin (henceforth, Mb) was measured.

[0039]

[0033] 3). The hollow filament was started from the dialyzer created like examples 1-6 and the example 1 of a comparison, 100 filament numbers and a mini module with a die length of 150mm were created, and the following analysis was performed per [which passed the sink and the mini module for 10ml of heparinize Homo sapiens fresh blood by the rate of flow of 1 ml/min to this] blood.

a) Platelet count (the electric resistance detecting method)

b) Heparin neutralizing substance (following PF- 4, enzyme immunity analysis)

c) C3a (radiation immunity analysis two antibody method)

d) Bradykinin (radiation immunity analysis PEG Following BK, law)

e) Granulocyte elastase (enzyme immunity analysis)

The result of having measured the result measured about each dialyzer by the mini module to Table 2 is shown in Table 3.

[0040]

[0034] Table 2 and 3 shows the measured value of each examples 1-6 at the time of setting measured value of the example 1 of a comparison to 100.

[0041]

[0035]

[0042]
[Table 2]

	uPR	クリアランス		
		クレアチニン	VB_{12}	Mb
実施例1	103	100	99	104
実施例2	72	97	101	76
実施例3	60	99	97	65
実施例4	98	99	97	105
実施例5	70	102	104	81
実施例6	64	98	98	68
比較例1	100	100	100	100

[0043]
[0036]
[0044]
[Table 3]

	血小板数	PF-4	C3a	BK	顆粒球エラスターゼ
実施例1	140	38	12	32	70
実施例2	152	27	8	26	75
実施例3	157	26	5	19	64
実施例4	143	45	18	42	68
実施例5	150	36	11	33	59
実施例6	166	21	7	20	62
比較例1	100	100	100	100	100

Maintaining the engine performance of a dialyzer, as by having insolubilized PVP and having held physically to the cellulose internal surface from the result of examples 1-6 and the example 1 of a comparison shows to Table 2, as shown in Table 3, there is little reduction in a platelet, and it turns out that emission of a heparin neutralizing substance, generation of C3a, generation of bradykinin, and emission of granulocyte elastase are controlled sharply.
[0045]
[0037]
[0046]
[Effect of the Invention] The vital reaction by contact to blood, such as a blood residual in a hollow filament, activation of complement, leuco PENIA, macromolecule kininogen activation, and a granulocyte stimulus, and a semipermeable hollow filament according [the reforming hollow filament described above according to this invention like] to platelet adhesion was controlled, the good hollow filament of haemocompatibility was obtained, and medical supplies, such as hemodialyzer using this invention reforming hollow filament, a hemofiltration machine, and a constituent-of-blood selection separation filter, turned into a good medical device of haemocompatibility with few stimuli to blood.

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TECHNICAL FIELD

[Industrial Application] This invention relates to the hollow filament by which reforming was carried out, and its manufacture approach. Furthermore, it is related with the reforming hollow filament biocompatibility and whose haemocompatibility improved, and its manufacture approach in detail by making the hydrophilic high polymer of a semipermeable hollow filament which insolubilized in water to the internal surface at least hold physically.
[0003]
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PRIOR ART

[Description of the Prior Art] The technique of using the film which has alternative permeability progresses splendidly in recent years, and utilization in extensive fields, such as a separation filter of a gas or a liquid, hemodialyzer in the medical field, a hemofiltration machine, and a constituent-of-blood selection separation filter, is progressing.
[0005]
[0003] Since especially the hollow filament-like film can make small occupied volume per film surface product, it miniaturizes andis [lightweight-] easy toize it, and it is used suitably. As a film ingredient, polymers, such as cellulose systems (a regenerated-cellulose system, a cellulose acetate system, chemistry denaturation cellulose system, etc.), a polyacrylonitrile system, a polymethylmethacrylate system, an ethylene vinyl alcohol system, and a polyamide system, have been used.
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EFFECT OF THE INVENTION

[Effect of the Invention] The vital reaction by contact to blood, such as a blood residual in a hollow filament, activation of complement, leuco PENIA, macromolecule kininogen activation, and a granulocyte stimulus, and a semipermeable hollow filament according [the reforming hollow filament described above according to this invention like] to platelet adhesion was controlled, the good hollow filament of haemocompatibility was obtained, and medical supplies, such as hemodialyzer using this invention reforming hollow filament, a hemofiltration machine, and a constituent-of-blood selection separation filter, turned into a good medical device of haemocompatibility with few stimuli to blood.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] However, when contacting the hollow filament used conventionally into blood, it is known by extent with the thick ingredient that a difference will occur a vital reaction between the constituent of blood of a certain thing of a certain kind and a film front face.
[0008]
[0005] For example. in the case of a cellulose system hollow filament, the alternative pathway of complement is activated, and when C3a which is anaphylatoxin is made to generate or it is used as a dialyzer, temporary reduction of the leucocyte in peripheral blood liquid is caused.
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[0007] the elastase which is the protease which there are many amounts of adhesion of a platelet in the case of a polymethylmethacrylate system hollow filament, is said for blood to tend to remain in the hollow filament after extracorporeal circulation termination of blood when it uses as a dialyzer, and occurs emission of granulocyte -- dialysis -- the crown -- becoming a value is also known.
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[0008] It is indicated that there is activation of complement classical pathway in the case of an ethylene vinyl alcohol system hollow filament.
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[0010] Thus, when the hollow filament used from the former was used as it was, the vital reaction occurred between a certain kind of constituent of blood, and the film front face, it has had a bad influence on it to blood not a little, and, for that reason, fewer hollow filaments of the vital reaction to a constituent of blood were desired.
[0014]
[0011]
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MEANS

[Means for Solving the Problem] this invention persons solve the trouble which the hollow filament which exists from the above-mentioned former has. The result of having repeated research wholeheartedly in order to obtain fewer hollow filaments of the vital reaction on a certain kind of constituent of blood, and the front face of a hollow fiber, By making the hydrophilic high polymer of a semipermeable hollow filament which insolubilized in water to the internal surface (front face in contact with blood) at least hold physically, it came to constitute a header and this invention for the vital reaction of a constituent of blood and an internal surface being improved a surprising degree.
[0016]
[0012] That is, this invention is a semipermeable hollow filament, and about the reforming hollow filament characterized by holding physically the hydrophilic high polymer insolubilized by the internal surface to water at least, after [a semipermeable hollow filament] contacting a hydrophilic high polymer to an internal surface at least, it relates to the manufacture approach of the reforming hollow filament characterized by constructing a bridge in this hydrophilic high polymer.
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[0013] Especially with the semipermeable hollow filament said here, by what is limited by the ingredient. a configuration, a dimension. the fractionation property, etc., there is nothing and hemodialysis, a protein fraction, plasma skimming, etc. should just choose a suitable thing in the light of the purpose.
[0018]
[0014] If an ingredient is illustrated, polymers, such as cellulose systems, such as a regenerated-cellulose system, a cellulose acetate system, and a chemistry denaturation cellulose system, a polyacrylonitrile system, a polymethylmethacrylate system, a polyvinyl system containing an ethylene-vinylalcohol copolymer, a polyamide system, a polyester system, and a polyolefine system, are mentioned, especially, a cellulose system polymer will have a strong mechanical strength, and thin-film-izing of a hollow fiber will be possible for it, and it will be used suitably.
[0019]
[0015] Although a cylinder-like object is usually used, a configuration The object of the configuration where the fin was attached to the cylindrical lateral surface can also be used. A dimension Thickness can use 5-50 micrometers and a bore can use preferably 1-100 micrometers of 50-500 micrometers of about 100-300-micrometer objects. About a fractionation property By the application, if it is an object for dialysis, if the permeability of the matter of molecular weight smaller than albumin is a high hollow filament and an object for protein fractions, low-molecular protein will penetrate from the low-molecular-weight matter. If it is the hollow filament and the object for plasma skimming which neither macromolecule protein nor matter like an immune complex can penetrate easily, although a plasma component will be penetrated, the hollow filament which does not penetrate a corpuscle component is used suitably.
[0020]
[0016] Moreover, although the matter which is meltable in water as for a hydrophilic high polymer, and

constructs a bridge by physical processing and/or chemical preparation, and can insolubilize [as opposed to / by that cause / water] is said and ******, a polyvinyl pyrrolidone, a polyethylene glycol, polyvinyl alcohol, a polypropylene glycol, etc. are mentioned, it is not limited to these, and it can recommend especially from the field of a biocompatibility improvement of a polyvinyl pyrrolidone and/or a polyethylene glycol in these.
[0021]
[0017] Viscosity although bridge formation tended to progress, when the larger one makes it a water solution becomes high, and it is hard coming to deal with the molecular weight of a hydrophilic high polymer. therefore -- as those molecular weight -- 500 to 1 million -- they are 10,000 to 500,000, and the thing which 20,000 to 400,000 can recommend still more preferably preferably.
[0022]
[0018] It is [of being divided] **** in the solubility over water that a hydrophilic high polymer is insolubilized to water, as a result of constructing a bridge over the above-mentioned hydrophilic high polymer and macromolecule-izing further.
[0023]
[0019] Moreover, that a hydrophilic high polymer is held physically at least at the internal surface The hydrophilic high polymer insolubilized to water exists near the front face of a semipermeable hollow filament. The hydrophilic high polymer underwater insolubilized to elution, the condition not separating, and which is held like, or water infiltrates into the interior of a semipermeable hollow filament in part. Without saying the condition of being mechanically held near the semipermeable hollow filament front face, and limiting a hydrophilic macromolecule's existence part only to an internal surface, even if it exists in parts other than this, for example, an outside surface, it does not interfere.
[0024]
[0020] The approach of contacting a hydrophilic high polymer to a semipermeable hollow filament A hydrophilic high polymer is contacted to the back semipermeable hollow filament dissolved in water, suitable solvents, or these mixed solvents. The approach of blowing away a solution excessive after that with a gas, the method of spraying the hydrophilic polymer solution which made it the shape of a fog on a semipermeable hollow filament, etc., Processing which could use the well-known coating approach and was described above may be performed in the state of a hollow filament, and you may carry out, after changing a hollow filament into the condition of modules, such as a dialyzer, a protein fraction Mr. filter, etc. with which the container was filled up.
[0025]
[0021] Although the concentration of a hydrophilic polymer solution can be chosen as arbitration in consideration of the filtration efficiency of the solution viscosity when carrying out to the molecular weight of a hydrophilic high polymer, i.e., a solution, and the semipermeable hollow filament after bridge formation etc., 0.1 to 1% of the weight of solution concentration can recommend [0.05] it still more preferably 5% of the weight preferably 10% of the weight from 0.01.
[0026]
[0022] If the approach of making a hydrophilic high polymer constructing a bridge is illustrated, in order to mention the radiation-induced crosslinking method using a gamma ray, an X-ray, etc., an ultraviolet-rays cross-linking method, a heat cross-linking method, the approaches using a crosslinking reagent. or such combination and to promote bridge formation, Various initiators, an initiation assistant or a polymerization nature monomer, oligomer, a polymer, etc. can also be used, and since there is little effect which it has on the membrane structure of a semipermeable hollow filament among the above-mentioned cross-linking methods and there are few problems of a residual reagent, especially a radiation-induced crosslinking method can recommend.
[0027]
[0023] Although selection of the dosage can select extent of bridge formation of a hydrophilic macromolecule, and extent of degradation of a material to a scale at arbitration when using a gamma ray among radiation-induced crosslinking methods, it is the dosage which 10 to 25kG(ies) can recommend still more preferably 50 kGies from 5 preferably 100 kGies from 1.

[0028]
[0024] As for the reforming hollow filament of this invention, it is common that the a large number book is used for a container in the form of the module by which adhesion immobilization was carried out, and it ** and explains it to drawing 1 hereafter taking the case of a dialyzer. Although drawing 1 is the mimetic diagram showing an example of a dialyzer, the a large number book converges on the dialysing fluid entrance 5 and the container 2 which has 5', an edge pastes up by potting material 3 like urethane, and the reforming hollow filament 1 is fixed to a container.
[0029]
[0025] A part for the centrum of the reforming hollow filament 1 is wide opened by a blood access 4 and 4', blood has the structure of flowing the inside of a reforming hollow filament, and the number of the reforming hollow filament 1 does not have them here what is limited to this range, although 1000 to 20000 and effective length have the common range of 150 to 400mm. Dialysing fluid enters from inlet-port 5', contacts the outside surface of the reforming hollow filament 1, and is discharged from an outlet 5, and the usage of blood of being discharged from the back outlet 4 which entered from inlet-port 4', entered in the reforming hollow filament 1, and was dialyzed is common. Although blood contacts the inside of the reforming hollow filament 1 The frequency where the front face and blood of the ingredient itself of the semipermeable hollow filament structure contact directly since the layer of a hydrophilic high polymer is formed in reforming hollow filament 1 internal surface is stopped low. As the result When the vital reaction of the fault which it is thought that the vital reaction between blood - film ingredients is controlled by it a surprising degree, consequently each film ingredient front face has, i.e., blood, has been improved, the fractionation property which each film ingredient has can be demonstrated enough.
[0030]
[0026]

[Translation done.]

EXAMPLE

[Example]
The dialyzer shown in drawing 1 , using a cuprammonium rayon ammonium cellulose hollow filament as examples 1-6 and an example of comparison 1 semipermeable hollow filament was made as an experiment.
[0032]
[0027] this dialyzer -- the thickness of 15 micrometers of a hollow filament, the bore of 180 micrometers, and the number of filaments -- 11000 and film surface product 1.5m2 it is -- to this dialyzer, polyvinyl-pyrrolidone (Following PVP is called.) processing was performed as a hydrophilic polymeric material, and it considered as examples 1-6. The processing condition is shown in Table 1.
[0033]
[0028]
[0034]
[Table 1]

	PVP 分子量	PVP濃度 (重量%)	γ線線量 (kGy)
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実施例3	4万	5.0	10
実施例4	36万	0.02	10
実施例5	36万	0.1	10
実施例6	36万	1.0	10

PVP used the thing of molecular weight 40,000 and molecular weight 360,000, and prepared the water solution of the concentration shown in Table 1, respectively. After pouring 200ml of each PVP solutions from blood inlet-port 4' to each unsettled dialyzer by the 800ml rate of flow for /, the PVP solution which remains by the 0.2kg/cm2 compressed air was blown away, and it discharged from the blood outlet 4. The gamma ray of next 10kGy was irradiated. Next, it was filled up with the inside of a hollow filament, and an outside, i.e., the container 2 interior, with water, and considered as the dialyzer of examples 1-6.
[0035]
[0029] On the other hand, the dialyzer which does not perform PVP processing was made into the example 1 of a comparison.
[0036]
[0030] The following trials were performed about the examples 1-6 and the example 1 of a comparison which were created as mentioned above.
[0037]

[0031] 1). In accordance with the performance-evaluation criteria of Japanese Society for Artificial Organs, the path clearance (value at the time of pressure 0mmHg between film) of the amount of water penetration (the unit omitted Following uFR is ml/hr/mmHg), a creatinine, and vitamin B12 (henceforth, VB 12) was measured.
[0038]
[0032] 2). According to the performance-measurement criteria of Japanese Society for Artificial Organs, the path clearance (however, value at the time of pressure 0mmHg between film) of a myoglobin (henceforth, Mb) was measured.
[0039]
[0033] 3). The hollow filament was started from the dialyzer created like examples 1-6 and the example 1 of a comparison, 100 filament numbers and a mini module with a die length of 150mm were created. and the following analysis was performed per [which passed the sink and the mini module for 10ml of heparinize Homo sapiens fresh blood by the rate of flow of 1 ml/min to this] blood.
a) Platelet count (the electric resistance detecting method)
b) Heparin neutralizing substance (following PF- 4, enzyme immunity analysis)
c) C3a (radiation immunity analysis two antibody method)
d) Bradykinin (radiation immunity analysis PEG Following BK, law)
e) Granulocyte elastase (enzyme immunity analysis)
The result of having measured the result measured about each dialyzer by the mini module to Table 2 is shown in Table 3.
[0040]
[0034] Table 2 and 3 shows the measured value of each examples 1-6 at the time of setting measured value of the example 1 of a comparison to 100.
[0041]
[0035]
[0042]
[Table 2]

	uFR	クリアランス		
		クレアチニン	VB_{12}	Mb
実施例1	103	100	99	104
実施例2	72	97	101	76
実施例3	60	99	97	63
実施例4	98	99	97	105
実施例5	70	102	104	81
実施例6	64	98	98	68
比較例1	100	100	100	100

[0043]
[0036]
[0044]
[Table 3]

	血小板数	PF-4	C3a	BK	顆粒球エラスターゼ
実施例1	140	32	12	32	70
実施例2	162	27	8	26	76
実施例3	157	26	5	19	64
実施例4	143	45	18	42	68
実施例5	160	35	11	33	59
実施例6	166	21	7	20	62
比較例1	100	100	100	100	100

Maintaining the engine performance of a dialyzer, as by having insolubilized PVP and having held physically to the cellulose internal surface from the result of examples 1-6 and the example 1 of a comparison shows to Table 2, as shown in Table 3, there is little reduction in a platelet, and it turns out that emission of a heparin neutralizing substance, generation of C3a, generation of bradykinin, and emission of granulocyte elastase are controlled sharply.
[0045]
[0037]

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is the mimetic diagram showing an example of the dialyzer using this invention reforming hollow filament.
[Description of Notations]
1 Reforming Hollow Filament
2 Container
3 Potting Material
4 Blood Outlet
4' Blood inlet port
5 Dialysing Fluid Outlet
5' Dialysing fluid inlet port

[Translation done.]

* NOTICES *

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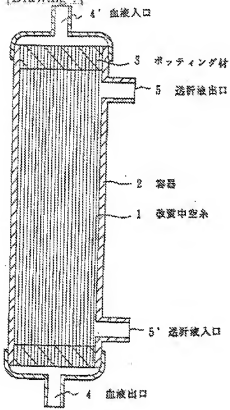
DRAWINGS

[Drawing 1]



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(56)参考文献　特開　平４－212372（ＪＰ，Ａ）
特開　平３－65225（ＪＰ，Ａ）
特開　平４－300638（ＪＰ，Ａ）

最終頁に続く

(54)【発明の名称】　改質中空糸およびその製造方法

1

(57)【特許請求の範囲】
【請求項１】　血液透析又は蛋白分画又は血漿分離に用いられる半透性中空糸の少なくとも内表面に親水性高分子物質を架橋させた後、該親水性高分子物質を架橋することを特徴とする改質中空糸の製造方法。
【請求項２】　架橋する方法が放射線架橋であることを特徴とする請求項１に記載の改質中空糸の製造方法。
【請求項３】　請求項１または２に記載の製造方法によって得られた改質中空糸であって、その表面近傍に水に対して不溶化された親水性高分子物質を物理的に保持していることを特徴とする改質中空糸。
【請求項４】　改質中空糸がセルロース系中空糸であることを特徴とする請求項３に記載の改質中空糸。
【請求項５】　親水性高分子物質がポリビニルピロリドンおよび／またはポリエチレングリコールであることを

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特徴とする請求項４に記載の改質中空糸。
【発明の詳細な説明】
【０００１】
【０００１】
【０００２】
【産業上の利用分野】本発明は、改質された中空糸およびその製造方法に関する。更に詳しくは、半透性中空糸の少なくとも内表面に対し、水に不溶化した親水性高分子物質を物理的に保持させることにより、生体適合性、血液適合性の向上した改質中空糸およびその製造方法に関する。
【０００３】
【０００２】
【０００４】
【従来の技術】近年、選択的な透過性を有する膜を利用

する技術がめざましく進歩し、気体や液体の分離フィルター，医療分野に於ける血液透析器，血液濾過器，血液成分選択分離フィルター等広範な分野での実用化が進んでいる。

【０００５】

【０００３】特に中空糸状の膜は、膜面積当りの占有体積を小さくできるので小型化，軽量化し易く，好適に用いられている。膜材料としては，セルロース系（再生セルロース系，酢酸セルロース系，化学変性セルロース系等），ポリアクリロニトリル系，ポリメチルメタクリレート系，エチレンビニルアルコール系，ポリアミド系等のポリマーが用いられてきた。

【０００６】

【０００４】

【０００７】

【発明が解決しようとする課題】しかしながら，従来用いられてきた中空糸は血液と接触させた時，原材料によって程度に差はあるものの或る種の血液成分と膜表面との間に生体反応を生起することが知られている。

【０００８】

【０００５】例えばセルロース系中空糸の場合は補体の副経路を活性化し、アナフィラトキシンであるＣ３ａを生成させたり，透析器として使用した際には末梢血液中の白血球の一時的減少を引き起こす。

【０００９】

【０００６】ポリアクリロニトリル系中空糸の場合は高分子キニノーゲンを活性化し、ブラジキニンを生成すると言われている。

【００１０】

【０００７】ポリメチルメタクリレート系中空糸の場合は血小板の粘着量が多く、透析器として用いた場合，血液の体外循環終了後の中空糸内に血液が残留し易いと言われており、また顆粒球の放出を生起するプロテアーゼであるエラスターゼが透析中高値になることも知られている。

【００１１】

【０００８】エチレンビニルアルコール系中空糸の場合は、補体古典経路の活性化があると指摘されている。

【００１２】

【０００９】ポリアミド系中空糸の場合は、やはり血小板の粘着量が多く、中空糸内への血液残留量が多い。

【００１３】

【００１０】この様に従来から使用されて来た中空糸をそのまま使用した場合には，或る種の血液成分と膜表面との間に生体反応が起こり、少なからず血液に対して悪影響を与えており、その為，血液成分に対する生体反応のより少ない中空糸が望まれていた。

【００１４】

【００１１】

【００１５】

【課題を解決するための手段】本発明者らは、上記した従来から在る中空糸が有する問題点を解決し、或る種の血液成分と中空糸膜表面との生体反応のより少ない中空糸を得るために鋭意研究を重ねた結果、半透性中空糸の少なくとも内表面（血液と接触する表面）に対して水に不溶化した親水性高分子物質を物理的に保持させる事により、血液成分と内表面との生体反応が驚くべき程改善されることを見出し、本発明を構成するに至った。

【００１６】

【００１２】すなわち本発明は、半透性中空糸であって、少なくともその内表面に水に対して不溶化された親水性高分子物質を物理的に保持していることを特徴とした改質中空糸に関するものであり、半透性中空糸の少なくとも内表面に親水性高分子物質を接触させた後，該親水性高分子物質を架橋することを特徴とした改質中空糸の製造方法に関するものである。

【００１７】

【００１３】ここで言う半透性中空糸とは、その材料，形状，寸法，分画特性等により特に限定されるものでは無く、血液透析，蛋白分画，血漿分離等，その目的に照らして適切なものを選択すれば良い。

【００１８】

【００１４】材料を例示すると，再生セルロース系，酢酸セルロース系，化学変性セルロース系等のセルロース系，ポリアクリロニトリル系，ポリメチルメタクリレート系，エチレンビニルアルコール共重合体を含むポリビニル系，ポリアミド系，ポリエステル系，ポリオレフィン系等のポリマーが挙げられ、中でもセルロース系ポリマーは，機械的強度が強く，中空糸膜の薄膜化が可能であり、好適に用いられる。

【００１９】

【００１５】形状は通常円筒状の物が用いられるが，円筒の外側面にフィンの付いた形状の物も使用することができ、寸法は，膜厚が１～１００μｍ，好ましくは５～５０μｍ，内径が５０～５００μｍ，好ましくは１００～３００μｍ程度の物が使用でき、分画特性については，その用途により透析用であれば低分子量物質からアルブミンより小さい分子量の物質の透過性が高い中空糸，蛋白分画用であれば低分子蛋白が透過し，高分子蛋白や免疫複合体の様な物質が透過し難い中空糸，血漿分離用であれば血漿成分は透過するが血球成分は透過しない中空糸などが好適に用いられる。

【００２０】

【００１６】また親水性高分子物質とは、水に可溶であり、かつ物理的処理および／または化学的処理により架橋し，それにより水に対し不溶化し得る物質を言い，例示すると，ポリビニルピロリドン，ポリエチレングリコール，ポリビニルアルコール，ポリプロピレングリコールなどが挙げられるが，これらに限定されるものではなく，これらの中では，ポリビニルピロリドンおよび／または

ポリエチレングリコールが生体適合性改善の面から特に推奨しうるものである。

【００２１】

【００１７】親水性高分子物質の分子量は大きい方が架橋が進み易いが、水溶液にした時の粘度が高くなり取り扱いにくくなる。したがって、それらの分子量としては、５００から１００万、好ましくは１万から５０万、更に好ましくは２万から４０万が推奨しうるものである。

【００２２】

【００１８】親水性高分子物質が水に対し不溶化されるということは、上記した親水性高分子物質が架橋され、更に高分子化した結果水に対する溶解性が失なわれるということである。

【００２３】

【００１９】また、少なくともその内表面に親水性高分子物質が物理的に保持されるということは、水に対し不溶化された親水性高分子物質が半透性中空糸の表面近傍に存在し、水中に溶出あるいは凝離して行かない様に保持されている状態、あるいは水に対し不溶化された親水性高分子物質が半透性中空糸内部に一部浸入し、半透性中空糸表面近傍に機械的に保持されている状態を言い、また、親水性高分子の存在部位は内表面のみに限定されることなく、これ以外の部位、例えば外表面に存在しても差支えない。

【００２４】

【００２０】親水性高分子物質を半透性中空糸に接触させる方法は、親水性高分子物質を水または適当な溶媒、あるいはこれらの混合溶媒に溶解させた後半透性中空糸に接触させ、その後余分な溶液を気体により吹き飛ばしてしまう方法、霧状にした親水性高分子溶液を半透性中空糸に吹き付ける方法等、公知のコーティング方法を使用することができ、また、上記した処理は、中空糸の状態で行なっても良いし、中空糸を容器に充填した透析器、血白分画膜濾過器等モジュールの状態にした後に行なってもよい。

【００２５】

【００２１】親水性高分子溶液の濃度は、親水性高分子物質の分子量、すなわち溶液にした時の溶液粘度、架橋後の半透性中空糸の濾過性能等を考慮して任意に選択しうるが、０．０１から１０重量％、好ましくは０．０５から５重量％、更に好ましくは０．１から１重量％の溶液濃度が推奨しうるものである。

【００２６】

【００２２】親水性高分子物質を架橋させる方法を例示すると、γ線、Ｘ線等を用いる放射線架橋法、紫外線架橋法、熱架橋法、架橋試薬を用いる方法あるいはこれらの組み合わせ等が挙げられ、また、架橋を促進させるため、種々の開始剤、開始助剤あるいは重合性モノマー、オリゴマー、ポリマー等を使用することもでき、上記した架橋法のうち、半透性中空糸の膜構造に与える影響が少なく、残留試薬の問題が少ないことなどから放射線架橋法が特に推奨しうるものである。

【００２７】

【００２３】放射線架橋法のうちγ線を用いる場合、その線量の選択は親水性高分子の架橋の程度、素材の劣化の程度を尺度に任意に選定できるが、１から１００ｋＧｙ、好ましくは５から５０ｋＧｙ、更に好ましくは１０から２５ｋＧｙが推奨しうる線量である。

【００２８】

【００２４】本発明の改質中空糸は、その多数本が容器に接着固定されたモジュールの形で使用されるのが一般的であり、以下、透析器を例にとり図１に則して説明する。図１は透析器の一例を示す模式図であるが、改質中空糸１は透析液出入口５，５′を有する容器２にその多数本が集束され、ウレタンの様なポッティング材３により端部が接着され、容器に固定される。

【００２９】

【００２５】改質中空糸１の中空部分は血液出入口４，４′に開放されており、血液は改質中空糸の内側を流れる構造になっており、ここで改質中空糸１の本数は１０００から２００００本、有効長は１５０から４００ｍｍの範囲が一般的であるがこの範囲に限定されるものでは無い。透析液は入口５′から入り、改質中空糸１の外表面に接触し、出口５から排出され、血液は入口４′から入り、改質中空糸１内に入り透析された後出口４から排出されるという使い方が一般的である。血液は改質中空糸１の内面に接触するわけであるが、改質中空糸１内表面には親水性高分子物質の層が形成されているので半透性中空糸構造体の材料そのものの表面と血液とが直接接触する頻度が低く抑えられ、その結果として、血液一膜材料間の生体反応が緩やべき得抑制されるものと思われ、その結果、各膜材料表面が持っている欠点、即ち血液との生体反応を改善したので、各膜材料の有している分画特性を充分発揮しうるものである。

【００３０】

【００２６】

【００３１】

【実施例】

実施例１～６および比較例１

半透性中空糸としてキュプラアンモニウムセルロース中空糸を用い図１に示す透析器を試作した。

【００３２】

【００２７】該透析器は、中空糸の膜厚１５μｍ、内径１８０μｍ、フィラメント数１１０００本、膜面積１．５ｍ^{2}であり、この透析器に対して、親水性高分子物質としてポリビニルピロリドン（以下ＰＶＰと称す。）処理を施して実施例１～６とした。表１にその処理条件を示す。

【００３３】

【００２８】
【００３４】
【表１】

	ＰＶＰ分子量	ＰＶＰ濃度（重量％）	γ線線量（ｋＧｙ）
実施例１	4万	0.1	10
実施例２	4万	1.0	10
実施例３	4万	5.0	10
実施例４	36万	0.02	10
実施例５	36万	0.1	10
実施例６	36万	1.0	10

ＰＶＰは分子量４万および分子量３６万のものを使用し、それぞれ表１に示す濃度の水溶液を調製した。それぞれの未処理透析器に対し血液入口４′から各々のＰＶＰ溶液２００ｍｌを８００ｍｌ／分の流速で流した後０．２ｋｇ／ｃｍ^{2}の圧縮空気で残存するＰＶＰ溶液を吹き飛ばして血液出口４から排出した。この後１０ｋＧｙのγ線を照射した。次に中空糸の内側，外側すなわち容器２内部を水で充填して実施例１～６の透析器とした。

【００３５】
【００２９】これに対して、ＰＶＰ処理を施さない透析器を比較例１とした。
【００３６】
【００３０】以上の様にして作成した実施例１～６および比較例１について以下の試験を行なった。
【００３７】
【００３１】１），日本人工臓器学会の性能評価基準に従い、透水量（以下ｕＦＲと略す，単位はｍｌ／ｈｒ／ｍｍＨｇ），クレアチニンおよびビタミンB_{12}（以下ＶＢ$_{12}$）のクリアランス（膜間圧力０ｍｍＨｇの時の値）を測定した。
【００３８】
【００３２】２），日本人工臓器学会の性能測定基準に準にミオグロビン（以下Ｍｂ）のクリアランス（但し膜間圧力０ｍｍＨｇの時の値）を測定した。

＊【００３９】
【００３３】３），実施例１～６，比較例１と同様に作成した透析器より中空糸を切り出し、フィラメント数１００本，長さ１５０ｍｍのミニモジュールを作成し、これにヘパリン添加ヒト新鮮血液１０ｍｌをＩｍｌ／ｍｉｎの流速で流し、ミニモジュールを通過した血液につき以下の分析を行なった。
a）　血小板数（電気抵抗検出法）
b）　血小板第４因子（以下ＰＦ－４，酵素免疫分析）
c）　Ｃ３ａ（放射免疫分析２抗体法）
d）　ブラジキニン（以下ＢＫ，放射免疫分析ＰＥＧ法）
e）　顆粒球エラスターゼ（酵素免疫分析）
各透析器について測定した結果を表２に、ミニモジュールで測定した結果を表３に示す。
【００４０】
【００３４】表２および表３は比較例１の測定値を１００とした場合の各々の実施例１～６の測定値を示す。
【００４１】
【００３５】
【００４２】
【表２】

	ｕＦＲ	クリアランス		
		クレアチニン	ＶＢ$_{12}$	Ｍｂ
実施例１	103	100	99	104
実施例２	72	97	101	76
実施例３	60	99	97	63
実施例４	98	99	97	105
実施例５	70	102	104	91
実施例６	64	95	98	68
比較例１	100	100	100	100

【００４３】
【００３６】
【００４４】
【表３】

	血小板数	ＰＦ-４	Ｃ３ａ	ＢＫ	顆粒球エラスターゼ
実施例１	140	32	12	32	70
実施例２	162	27	8	26	76
実施例３	157	26	5	19	64
実施例４	142	45	18	42	68
実施例５	160	36	11	33	59
実施例６	156	21	7	20	62
比較例１	100	100	100	100	100

実施例１～６および比較例１の結果から、ＰＶＰを不溶化し、セルロース内表面に物理的に保持したことによ

り、表２に示す様に透析器の性能を維持しつつ、表３に示す様に血小板の減少が少なく、血小板第４因子の放出、Ｃ３ａの生成、ブラジキニンの生成，顆粒球エラスターゼの放出が大幅に抑制されていることが判る。

【００４５】

【００３７】

【００４６】

【発明の効果】以上述べた様に、本発明による改質中空糸は、血小板付着による中空糸内血液残留，補体の活性化，ロイコペニア，高分子キニノーゲン活性化，顆粒球刺激等血液と半透性中空糸との接触による生体反応が抑制され，血液適合性の良好な中空糸が得られ、本発明改質中空糸を用いた血液透析器，血液濾過器，血液成分選＊択分離フィルター等の医療用具は血液に対する刺激の少ない、血液適合性の良好な医療器具となった。

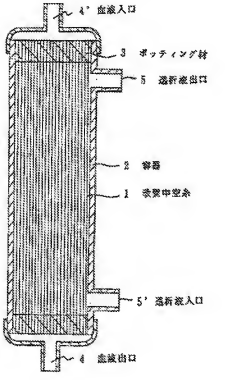
【図面の簡単な説明】

【図１】本発明改質中空糸を用いた透析器の一例を示す模式図である。

【符号の説明】

１　改質中空糸
２　容器
３　ポッティング材
４　血液出口
４′　血液入口
５　透析液出口
５′　透析液入口

【図１】



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1.This document has been translated by computer. So the translation may not reflect the original precisely.

2.**** shows the word which can not be translated.

3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]

[Claim 1] The refining hollow filament characterized by holding physically the hydrophilic polymeric material which is a semipermeable hollow filament and was insolubilized by the internal surface to water at least.

[Claim 2] The refining hollow filament of the application for patent characterized by a semipermeable hollow filament being a cellulose type hollow filament given in the 1st term of the range.

[Claim 3] The refining hollow filament of the application for patent characterized by hydrophilic polymeric materials being a polyvinyl pyrrolidone and/or a polyethylene glycol given in the 1st term of the range.

[Claim 4] The manufacture approach of the refining hollow filament characterized by constructing a bridge in this hydrophilic polymeric material after [a semipermeable hollow filament] contacting a hydrophilic polymeric material to an internal surface at least.

[Claim 5] The manufacture approach of the refining hollow filament of the application for patent characterized by the approach of constructing a bridge being radiation-induced crosslinking given in the 4th term of the range.

TECHNICAL FIELD

[Industrial Application] This invention relates to the hollow filament by which refining was carried out, and its manufacture approach. Furthermore, it is related with the refining hollow filament biocompatibility and whose haemocompatibility improved, and its manufacture approach in detail by making the hydrophilic polymeric material of a semipermeable hollow filament which insolubilized in water to the internal surface at least hold physically.

[0003]

[0002]

PRIOR ART

[Description of the Prior Art] The technique of using the film which has alternative

permeability progresses splendidly in recent years, and utilization in extensive fields, such as a separation filter of a gas or a liquid, hemodialyzer in the medical field, a blood filter, and a constituent-of-blood selection separation filter, is progressing.

[0005]

[0003] Since especially the hollow filament-like film can make small occupied volume per film surface product, it miniaturizes andis [lightweight-] easy toize it, and it is used suitably. As a film ingredient, polymers, such as cellulose types (a regenerated-cellulose system, a cellulose acetate system, chemistry denaturation cellulose type, etc.), a polyacrylonitrile system, a polymethylmethacrylate system, an ethylene vinyl alcohol system, and a polyamide system, have been used.

[0006]

[0004]

EFFECT OF THE INVENTION

[Effect of the Invention] The vital reaction by contact to blood, such as a blood residual in a hollow filament, activation of complement, leuco PENIA, macromolecule kininogen activation, and a granulocyte stimulus, and a semipermeable hollow filament according [the refining hollow filament described above according to this invention like] to platelet adhesion was controlled, the good hollow filament of haemocompatibility was obtained, and medical supplies, such as hemodialyzer using this invention refining hollow filament, a blood filter, and a constituent-of-blood selection separation filter, turned into a good medical device of haemocompatibility with few stimuli to blood.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] However, when contacting the hollow filament used conventionally into blood, it is known by extent with the thick ingredient that a difference will occur a vital reaction between the constituent of blood of a certain thing of a certain kind and a film front face.

[0008]

[0005] For example, in the case of a cellulose type hollow filament, the alternative pathway of complement is activated, and when C3a which is anaphylatoxin is made to generate or it is used as a dialyzer, temporary reduction of the leucocyte in peripheral blood liquid is caused.

[0009]

[0006] In the case of a polyacrylonitrile system hollow filament, giant-molecule kininogen is activated, and it is said that bradykinin is generated.

[0010]

[0007] the elastase which is the protease which there are many amounts of adhesion of a platelet in the case of a polymethylmethacrylate system hollow filament, is said for blood to tend to remain in the hollow filament after extracorporeal circulation termination of blood when it uses as a dialyzer, and occurs bleedoff of granulocyte ·· dialysis ·· the crown ·· becoming a value is also known.

[0011]

[0008] It is indicated that there is activation of complement classical pathway in the case of an ethylene vinyl alcohol system hollow filament.

[0012]

[0009] In the case of a polyamide system hollow filament, there are many amounts of adhesion of a platelet too, and there are many amounts of blood residuals into a hollow filament.

[0013]

[0010] Thus, when the hollow filament used from the former was used as it was, the vital reaction occurred between a certain kind of constituent of blood, and the film front face, it has had an adverse effect on it to blood not a little, and, for that reason, fewer hollow filaments of the vital reaction to a constituent of blood were desired.

[0014]

[0011]

MEANS

[Means for Solving the Problem] this invention persons solve the trouble which the hollow filament which exists from the above-mentioned former has. The result of having repeated research wholeheartedly in order to obtain fewer hollow filaments of the vital reaction on a certain kind of constituent of blood, and the front face of a hollow fiber, By making the hydrophilic polymeric material of a semipermeable hollow filament which insolubilized in water to the internal surface (front face in contact with blood) at least hold physically, it came to constitute a header and this invention for the vital reaction of a constituent of blood and an internal surface being improved a surprising degree.

[0016]

[0012] That is, this invention is a semipermeable hollow filament, and about the refining hollow filament characterized by holding physically the hydrophilic polymeric material insolubilized by the internal surface to water at least, after [a semipermeable hollow filament] contacting a hydrophilic polymeric material to an internal surface at least, it relates to the manufacture approach of the refining hollow filament characterized by constructing a bridge in this hydrophilic polymeric material.

[0017]

[0013] Especially with the semipermeable hollow filament said here, by what is limited by the ingredient, a configuration, a dimension, the fractionation property, etc., there is nothing and hemodialysis, a protein fraction, plasma skimming, etc. should just choose a suitable thing in the light of the object.

[0018]

[0014] If an ingredient is illustrated, polymers, such as cellulose types, such as a regenerated-cellulose system, a cellulose acetate system, and a chemistry denaturation cellulose type, a polyacrylonitrile system, a polymethylmethacrylate system, a polyvinyl system containing an ethylene-vinylalcohol copolymer, a polyamide system, a polyester system, and a polyolefine system, are mentioned, especially, a cellulose type polymer will have a strong mechanical strength, and thin-film-izing of a hollow fiber will be possible for it, and it will be used suitably.

[0019]

[0015] Although a cylinder-like object is usually used, a configuration The object of the configuration where the fin was attached to the cylindrical lateral surface can also be used. A dimension Thickness can use 5-50 micrometers and a bore can use preferably 1-100 micrometers of 50-500 micrometers of about 100-300-micrometer objects. About a fractionation property By the application, if it is an object for dialysis, if the permeability of the matter of molecular weight smaller than albumin is a high hollow filament and an object for protein fractions, low-molecular protein will penetrate from the low-molecular-weight matter. If it is the hollow filament and the object for plasma skimming which neither macromolecule protein nor matter like an immune complex can penetrate easily, although a plasma component will be penetrated, the hollow filament which does not penetrate a corpuscle component is used suitably.

[0020]

[0016] Moreover, although the matter which is meltable in water as for a hydrophilic polymeric material, and constructs a bridge by physical processing and/or chemical preparation, and can insolubilize [as opposed to / by that cause / water] is said and ******, a polyvinyl pyrrolidone, a polyethylene glycol, polyvinyl alcohol, a polypropylene glycol, etc. are mentioned, it is not limited to these, and it can recommend especially from the field of a biocompatibility improvement of a polyvinyl pyrrolidone and/or a polyethylene glycol in these.

[0021]

[0017] Viscosity although bridge formation tended to progress, when the larger one makes it a water solution becomes high, and it is hard coming to deal with the molecular weight of a hydrophilic polymeric material. therefore -- as those molecular weight -- 500 to 1 million -- they are 10,000 to 500,000, and the thing which 20,000 to 400,000 can recommend still more preferably preferably.

[0022]

[0018] It is [of being divided] **** in the solubility over water that a hydrophilic polymeric material is insolubilized to water, as a result of constructing a bridge over the above-mentioned hydrophilic polymeric material and macromolecule-izing further.

[0023]

[0019] Moreover, that a hydrophilic polymeric material is held physically at least at the internal surface The hydrophilic polymeric material insolubilized to water exists near the front face of a semipermeable hollow filament. The hydrophilic polymeric material underwater insolubilized to the condition which does not elute or separate, and which is held like, or water infiltrates into the interior of a semipermeable hollow filament in part. Without saying the condition of being mechanically held near the semipermeable hollow filament front face, and limiting a hydrophilic macromolecule's existence part only to an internal surface, even if it exists in parts other than this, for example, an outside surface, it does not interfere.

[0024]

[0020] The approach of contacting a hydrophilic polymeric material to a semipermeable hollow filament After dissolving a hydrophilic polymeric material in water, suitable solvents, or these mixed solvents, a semipermeable hollow filament is made to contact. The approach of blowing away a solution excessive after that with a gas, the method of spraying the hydrophilic polymer solution which made it the shape of a fog on a semipermeable hollow filament, etc., Processing which could use the well-known coating approach and was described above may be performed in the state of a hollow filament, and you may carry out, after changing a hollow filament into the condition of modules, such as a dialyzer, a protein fraction Mr. filter, etc. with which the container was filled up.

[0025]

[0021] Although the concentration of a hydrophilic polymer solution can be chosen as arbitration in consideration of the filtration efficiency of the solution viscosity when carrying out to the molecular weight of a hydrophilic polymeric material, i.e., a solution, and the semipermeable hollow filament after bridge formation etc., 0.1 to 1% of the weight of solution concentration can recommend [0.05] it still more preferably 5% of the weight preferably 10% of the weight from 0.01.

[0026]

[0022] If the approach of making a hydrophilic polymeric material constructing a bridge is illustrated, in order to mention the radiation-induced crosslinking method using a gamma ray, an X-ray, etc., an ultraviolet-rays cross-linking method, a heat cross-linking method, the approaches using a crosslinking reagent, or such combination and to promote bridge formation, Various initiators, an initiation assistant or a polymerization nature monomer, oligomer, a polymer, etc. can also be used, and since there is little

effect which it has on the membrane structure of a semipermeable hollow filament among the above-mentioned cross-linking methods and there are few problems of a residual reagent, especially a radiation-induced crosslinking method can recommend.

[0027]

[0023] Although selection of the dosage can select extent of bridge formation of a hydrophilic macromolecule, and extent of degradation of a raw material to a scale at arbitration when using a gamma ray among radiation-induced crosslinking methods, it is the dosage which 10 to 25kG(ies) can recommend still more preferably 50 kGies from 5 preferably 100 kGies from 1.

[0028]

[0024] As for the refining hollow filament of this invention, it is common that the a large number book is used for a container in the form of the module by which adhesion immobilization was carried out, and it ** and explains it to drawing 1 hereafter taking the case of a dialyzer. Although drawing 1 is the mimetic diagram showing an example of a dialyzer, the a large number book converges on the dialysing fluid gate 5 and the container 2 which has 5', an edge pastes up by potting material 3 like urethane, and the refining hollow filament 1 is fixed to a container.

[0029]

[0025] The hollow part of the refining hollow filament 1 is opened by a blood access 4 and 4', blood has the structure of flowing the inside of a refining hollow filament, and the number of the refining hollow filament 1 does not have them here what is limited to this range, although 1000 to 20000 and effective length have the common range of 150 to 400mm. Dialysing fluid enters from inlet-port 5', contacts the outside surface of the refining hollow filament 1, and is discharged from an outlet 5, and after blood enters from inlet-port 4', enters in the refining hollow filament 1 and is dialyzed, its usage of being discharged from an outlet 4 is common. Although blood contacts the inner surface of the refining hollow filament 1 The frequency where the front face and blood of the ingredient itself of the semipermeable hollow filament structure contact directly since the layer of a hydrophilic polymeric material is formed in refining hollow filament 1 internal surface is stopped low. As the result When the vital reaction of the fault which it is thought that the vital reaction between blood · film ingredients is controlled by it a surprising degree, consequently each film material-list side has, i.e., blood, has been improved, the fractionation property which each film ingredient has can be demonstrated enough.

[0030]

[0026]

EXAMPLE

[Example]

The dialyzer shown in drawing 1 , using a cuprammonium rayon ammonium cellulose hollow filament as examples 1-6 and an example of comparison 1 semipermeable hollow filament was made as an experiment.

[0032]

[0027] this dialyzer -- the thickness of 15 micrometers of a hollow filament, the bore of 180 micrometers, and the number of filaments -- 11000 and film surface product 1.5m2 it is -- to this dialyzer, polyvinyl-pyrrolidone (Following PVP is called.) processing was performed as a hydrophilic polymeric material, and it considered as examples 1-6. The processing condition is shown in a table 1.

[0033]

[0028]

[0034]

[A table 1]

	PVP 分子量	PVP濃度 (重量%)	γ線線量 (kGy)
実施例1	4万	0.1	10
実施例2	4万	1.0	10
実施例3	4万	5.0	10
実施例4	36万	0.02	10
実施例5	36万	0.1	10
実施例6	36万	1.0	10

PVP used the thing of molecular weight 40,000 and molecular weight 360,000, and prepared the water solution of the concentration shown in a table 1, respectively. After pouring 200ml of each PVP solutions from blood inlet-port 4' to each unsettled dialyzer by the 800ml rate of flow for /, the PVP solution which remains by the 0.2kg/cm2 compressed air was blown away, and it discharged from the blood outlet 4. The gamma ray of next 10kGy was irradiated. Next, it was filled up with the inside of a hollow filament, and an outside, i.e., the container 2 interior, with water, and considered as the dialyzer of examples 1-6.

[0035]

[0029] On the other hand, the dialyzer which does not perform PVP processing was made into the example 1 of a comparison.

[0036]

[0030] The following trials were performed about the examples 1-6 and the example 1 of a comparison which were created as mentioned above.

[0037]

[0031] 1). In accordance with the performance-evaluation criteria of Japanese Society for Artificial Organs, the path clearance (value at the time of pressure 0mmHg between film) of the amount of water penetration (the unit omitted Following uFR is ml/hr/mmHg), a creatinine, and vitamin B12 (henceforth, VB 12) was measured.

[0038]

[0032] 2). According to the performance-measurement criteria of Japanese Society for Artificial Organs, the path clearance (however, value at the time of pressure 0mmHg between film) of a myoglobin (henceforth, Mb) was measured.

[0039]

[0033] 3). The hollow filament was started from the dialyzer created like examples 1-6 and the example 1 of a comparison, 100 filament numbers and a mini module with a die length of 150mm were created, and the following analysis was performed per 1 which passed the sink and the mini module for 10ml of heparinize Homo sapiens fresh blood by the rate of flow of 1 ml/min to this blood.

a) Platelet count (the electric resistance detecting method)

b) Heparin neutralizing substance (following PF- 4, enzyme immunity analysis)

c) C3a (radiation immunity analysis two antibody method)

d) Bradykinin (radiation immunity analysis PEG Following BK, law)

e) Granulocyte elastase (enzyme immunity analysis)

The result of having measured the result measured about each dialyzer by the mini module to a table 2 is shown in a table 3.

[0040]

[0034] A table 2 and a table 3 show the measured value of each examples 1-6 at the time of setting measured value of the example 1 of a comparison to 100.

[0041]

[0035]

[0042]

[A table 2]

	uPR	クリアランス		
		クレアチニン	VB_{12}	Mb
実施例1	103	100	99	104
実施例2	72	97	101	76
実施例3	60	99	97	63
実施例4	98	99	97	105
実施例5	70	102	104	81
実施例6	64	98	98	68
比較例1	100	100	100	100

[0043]
[0036]
[0044]
[A table 3]

	血小板数	PF-4	C3a	BK	顆粒球エラスターゼ
実施例1	140	32	12	32	70
実施例2	162	27	8	26	76
実施例3	157	26	5	19	64
実施例4	143	45	18	42	68
実施例5	160	36	11	33	59
実施例6	166	21	7	20	62
比較例1	100	100	100	100	100

Maintaining the engine performance of a dialyzer, as by having insolubilized PVP and having held physically to the cellulose internal surface from the result of examples 1-6 and the example 1 of a comparison shows to a table 2, as shown in a table 3, there is little reduction in a platelet, and it turns out that bleedoff of a heparin neutralizing substance, generation of C3a, generation of bradykinin, and bleedoff of granulocyte elastase are controlled substantially.

[0045]

[0037]

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] It is the mimetic diagram showing an example of the dialyzer using this invention refining hollow filament.

[Description of Notations]

1 Refining Hollow Filament

2 Container

3 Potting Material

4 Blood Outlet

4' Blood inlet port

5 Dialysing Fluid Outlet

5' Dialysing fluid inlet port